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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/957,709	10/24/1997	HOLLY HOGREFE	1486/41363CP	2438

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	38

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	08/957,709	HOGREFE ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 November 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *07 November 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see atttached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *none*.

Claim(s) rejected: *17,46,59-66,77-79,85,87-92,95 and 97*.

Claim(s) withdrawn from consideration: *none*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

ADVISORY ACTION

1. Claims 17, 46, 59-66, 77-79, 85, 87-92, 95, 97 are pending.

2. Applicant's submission of page 43 in a communication filed on 11/7/2003 is acknowledged. While Applicants argue the propriety of the term "shading" as opposed to highlighting, it is noted that the alignment provided is objected to due to the fact that the specification in page 42, line 6 refers to the presence of gray boxes and black boxes in the alignment, and the alignment submitted on 11/7/2003 does not show gray boxes. All the boxes in this alignment are black. Appropriate correction is required.

3. The specification is objected for not complying with sequence rules. See specifically pages 41 (line 18) and 43 (entire page) which disclose sequences but lack a sequence identifier. Applicant is required to insert sequence identifiers in front of sequences referred to in the specification. If sequence identifiers cannot be placed physically in front of these sequences, the specification should indicate which are the sequence identifiers which correspond to the sequences displayed. See particularly 37 CFR 1.821(d). Appropriate correction is required.

4. The request for entering amendments to claims 90 and 95, cancellation of claims 24-27, 40-44, 47-58, 67-76, 80-84, 86, 93-94, and arguments filed on 11/7/2003 under 37 CFR 1.116 in reply to the Final Action Paper No. 33 mailed on 5/6/2003 are acknowledged. The proposed amendments to the claims will be entered since they are deemed sufficient to overcome the objections and the 35 USC 112, second paragraph rejection of claim 80 previously applied. However, entry of these amendments is not deemed sufficient to place the application in condition for allowance for the following reasons.

5. Claims 17 and 46 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These rejections have been discussed at length in Paper No. 33, mailed on 5/6/2003.

6. In regard to claim 17, Applicants submit that the claim is not indefinite in the recitation of "at least one subunit is a P. furiosus protein selected from at least one of" since the term "at least one subunit" may be more than one subunit, permitting a mixture of proteins. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. As indicated in the previous action, while it is clear that the protein complex may have more than one subunit, it is noted that the term "wherein at least one subunit is a P. furiosus protein" is defining the subunit which can be part of the complex, i.e. a P. furiosus protein.. As such, the "P furiosus protein" is a single protein. The term "selected from at least one of" implies that the P. furiosus protein can be a combination of several proteins, i.e. the ones recited immediately after the term "at least one of", which is unclear and confusing since it appears from the preamble that the P. furiosus protein is a single protein and not a mixture. It is noted that the mixture of proteins appear to be the protein complex recited in the preamble. Applicants request a suggestion. The Examiner previously suggested that the term "selected from at least one of" be replaced with "selected from the group consisting of". This language is clearly defining which P. furiosus proteins can be one of the many subunits the protein complex can have and does not affect the intended scope, which is a protein complex comprising more than one subunit. For examination purposes, the term "selected from the group consisting of" will be used instead. Correction is required.

7. In regard to claim 46, Applicants submit that the intended scope is an antibody which can bind a protein comprising both SEQ ID NO: 19 and 71, as well as a protein comprising either SEQ ID NO: 19 or SEQ ID NO: 71. For clarity, it is suggested that the term be amended to recite "antibody that binds to a protein comprising the amino acid sequence of SEQ ID NO: 19 and/or SEQ ID NO: 71". Appropriate correction is required.

8. Claims 80, 85, 87-92 and 97 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. This rejection has been discussed at length in Paper No. 33, mailed on 5/6/2003. Applicants argue that the Examiner's categorization of claim 85 as a genus claim is erroneous since it recites " SEQ ID NO: 73". Furthermore, Applicants submit that they have repeatedly demonstrated possession of the claimed invention by actual reduction to practice through the specification. Regarding claim 85, Applicants submit that even if this claim is generic, it still satisfy the written description requirement as it recites a structure, i.e. SEQ ID NO: 73.

9. Applicant's arguments regarding claim 85 have been considered but are not deemed persuasive to overcome the rejection. First, the claim is generic as it is not directed to a protein consisting of SEQ ID NO: 73 but rather to a group of proteins comprising the amino acid sequence of SEQ ID NO: 73. In addition, as indicated in previous Office Action Paper No. 33, the structural feature recited does not constitute a substantial portion of the genus of proteins claimed since the remainder of a protein comprising SEQ ID NO: 73 is completely undefined and the specification does not provide the remaining structural features necessary for members of the genus to be selected. It is reiterated herein that 14 amino acids (SEQ ID NO: 73) are not sufficient to adequately describe the genus of proteins having the function recited in view of the fact that there is no teaching indicating that this structural element is related to the function recited. The genus of proteins encompassed by the claim is a large structurally variable genus and the specification has not provided sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicants were in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within

the genus. Thus, one cannot reasonably conclude that the invention of claim 85 is adequately described. The rejection of claims 80, 87-92 and 97 is maintained for the reasons already discussed in Paper No. 33.

10. Claims 85, 87-92, and 97 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 71 (156 amino acids), does not reasonably provide enablement for (1) a polypeptide having polymerase enhancing factor activity comprising the amino acid sequence of SEQ ID NO: 73 (14 amino acids), (2) a composition or protein extract comprising a T. thermophilis dUTPase, (3) a composition or protein extract comprising T. thermophilis proteins and dUTPases from any source, (4) the composition/protein extract of (2) or (3) which comprises a protein of any function which can be detected by an antibody specific for the protein of SEQ ID NO: 71, (5) the composition/protein extract of (2), (3) or (4) further comprising a thermostable DNA polymerase, (6) the protein extract of (4) wherein the protein has a MW of 92 KDa, or (7) the protein extract of (2) or (3) which comprises a protein of any function having a MW of 24 KDa. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in Paper No. 33, mailed on 5/6/2003.

11. Applicants argue that known the critical structural elements required in a dUTPase or which regions of SEQ ID NO: 71 correlate with dUTPase activity are not necessary to successfully find a dUTPase in an antibody screen. According to Applicants, a protein with dUTPase activity may be selected by binding to an area that is not responsible for the actual dUTPase and selection of those proteins with the desired activity does not require undue experimentation. Applicants also submit that purification is not required to determine whether a putative protein possesses dUTPase activity and that the standard for enablement is undue experimentation. Applicants assert that isolation of polypeptides, analogs, and protein extract was routine in the art at the time of filing. Applicants submit that the Examiner has not shown how a higher structural homology between the polypeptide of SEQ ID NO: 1

and dCTPases has any effect on the ability to practice the claimed invention. Applicants point to *In re Wands* and indicate that that in that case the specification was found enabling even if the structures of the monoclonal antibodies were not predictable.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The Examiner acknowledges the teachings of the specification and the findings in *In re Wands*. However, the Examiner disagrees with Applicant's contention that the claimed invention is enabled for the full scope of the claims. It is noted that there is a potentially large number of antibodies which can bind to the polypeptide of SEQ ID NO: 71 as it is 154 amino acids long. In the absence of any correlation between SEQ ID NO: 71 and function, one of skill in the art would have no clue as to which antibodies are more likely to detect those proteins with the desired function. It is reiterated herein that while testing a limited number of samples would not constitute undue experimentation, testing an extremely large number of proteins to determine which ones have the desired activity would constitute undue experimentation absence some teaching correlating structure with function. In this case, knowing which structural elements in SEQ ID NO: 71 correlate with function would limit the number of antibodies which will be used to detect the desired proteins. Similarly, testing the extremely large number of polypeptides which comprise the peptide of SEQ ID NO: 73 would constitute undue experimentation absent any teaching as to whether the peptide of SEQ ID NO: 73 correlates with the desired activity.

It is noted that claims 87-92 and 97 are also directed to proteins from <u>any source</u> having dUTPase activity as the functional limitation recited refers to a protein extract which can comprise proteins which are not from T. thermophilis, i.e. the functional limitation is not just for T. thermophilis proteins. It is also noted that in claim 90, the protein in the protein extract which binds to an antibody specific for the polypeptide of SEQ ID NO: 71 can have <u>any</u> function. Even if one assumes that claim 90 recites a functional limitation (dUTPase activity) in regard to the protein which can be detected by the antibody, it

is worth noting that while the specification discloses an unspecified antibody raised against the polypeptide of SEQ ID NO: 71 (i.e. no epitope disclosed), which detects proteins in a Western blot having a T. thermophilis cell extract, there is no teaching in the specification as to which structural elements in the polypeptide of SEQ ID NO: 71 correlate with dUTPase activity such that one of skill in the art would know the antibodies most likely to detect a protein having dUTPase activity. It is also reiterated herein that the specification teaches that the polypeptide of SEQ ID NO: 71 shares higher structural similarity to a dCTPase, therefore suggesting that the polypeptide of SEQ ID NO: 71 is more likely to be a dCTPase. Thus, even if one assumes that any antibody which is specific for the polypeptide of SEQ ID NO: 71 would detect proteins of similar biological activity as that of the polypeptide of SEQ ID NO: 71, an antibody against the polypeptide of SEQ ID NO: 71 would not detect a dUTPase if the polypeptide of SEQ ID NO: 71 is a dCTPase. Since the specification fails to disclose whether the polypeptide of SEQ ID NO: 71 is indeed a dUTPase or a dCTPase, and which are the structural elements in the polypeptide of SEQ ID NO: 71 which are found in any dUTPase such that one would know which antibodies are more likely to detect proteins of similar function, one of skill in the art cannot reasonably conclude that enabling the full scope of the claims would only require routine experimentation.

13. Claim 80 was rejected under 35 U.S.C. 102(a) as being anticipated by Cohen et al. (Genomics 40(1):213-215, February 15, 1997; GenBank accession number U62891 (DNA) and AAC51123 (protein)) as evidenced by Hogrefe et al. (Proc. Natl. Acad. Sci. 99(2):596-601, 2002; cited in the IDS). In view of Applicant's cancellation of claim 80, this rejection is hereby withdrawn.

14. Claims 17, 46, 59-66, 77-79, 85, 87-92, 95, and 97 remain rejected under the judicially created doctrine of double patenting over claims 1, 5-9, 13-20, 23-24, 26-34 and 40-41 of U.S. Patent No. 6,183,997. This rejection has been discussed at length in Paper No. 25, mailed on 2/27/2002. Applicants have indicated that if the instant claims are found allowable, a terminal disclaimer will be filed. Since a terminal disclaimer has not yet been filed and no arguments have been presented pointing out

disagreements with the Examiner's contentions, the double patenting rejection is maintained for the reasons of record.

15. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: NONE

Claim(s) rejected: 17, 46, 59-66, 77-79, 85, 87-92, 95, and 97

Claim(s) withdrawn from consideration: NONE

16. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 16, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600